DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NOVEL ISOCHROMANONE DERIVATIVES AND TOTAL SYNTHESIS OF MACROCYCLIC NATURAL PRODUCTS

Synopsis

Of the Ph.D. Thesis to be submitted to the
MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF
DOCTOR OF PHILOSOPHY

IN
CHEMISTRY
By

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Title of the Thesis : DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NOVEL ISOCHROMANONE DERIVATIVES AND TOTAL SYNTHESIS OF MACROCYCLIC NATURAL PRODUCTS.

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SYNOPSIS

Nitrogen-containing compounds or heterocycles, which are essential building blocks found in various bioactive natural products, pharmaceuticals, agrochemicals, dyes, cosmetics, and functional materials, play a crucial role in modern science. Consequently, the synthesis of *N*-heterocycles and their derivatives has consistently captivated researchers in the field of organic synthesis due to their significance. The synthetic community has shown particular interest in these compounds due to their prevalence in natural products, particularly alkaloids. As a result, a vast number of nitrogen compounds have been studied in pharmaceutical and agrochemical research.[1] Structural characteristics such as interaction with proteins *via* H-bonding result in biological activity. FDA databases have revealed that about 60% of unique small-molecule drugs include *N*-based heterocycles, showing the structural significance of *N*-based heterocycles in agrochemical discovery and drug discovery.[2]

In this context, the current research work explored to develop a novel route and to synthesize novel molecules, and subsequently evaluated for their potential applications in agrochemicals. The topic of the thesis is entitled "Design, Synthesis and Biological Activity of Some Novel Isochromanone Derivatives and Total Synthesis of Macrocyclic Natural Products". This work has been divided into the following four chapters.

Chapter 1: Development of novel methodology for the synthesis of carbamates and application of carbamates towards the synthesis of isochromanones

1.1 Introduction to carbamate

This section provides a concise overview of carbamates and their significance as the widely prevalent carbamate functional group found in various natural products,[3] pharmaceuticals,[4] agrochemicals,[5] protecting groups utilized in peptide synthesis,[6] and intermediates involved in numerous organic syntheses.[7] Few of the agrochemically important carbamates are listed in **Figure 1**.

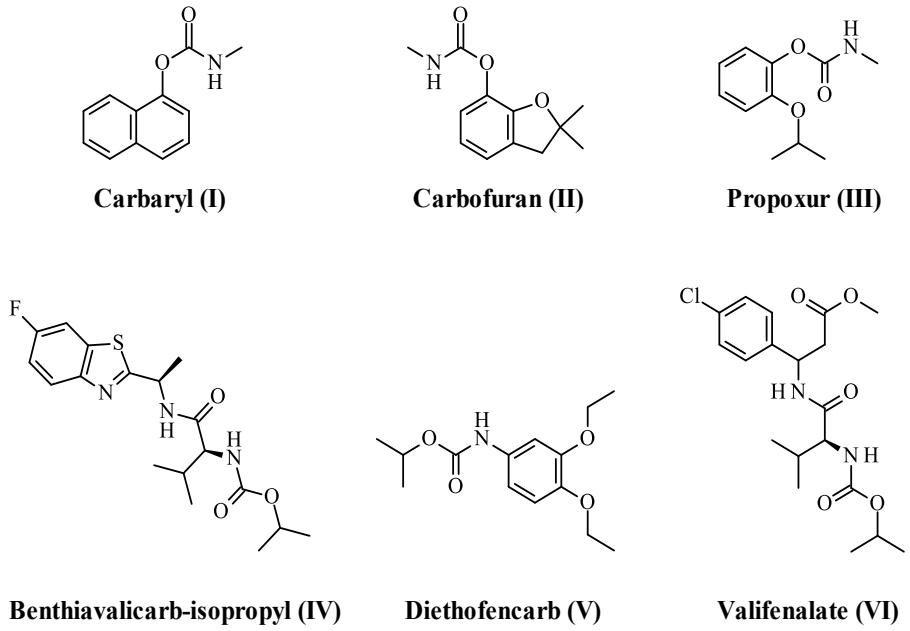


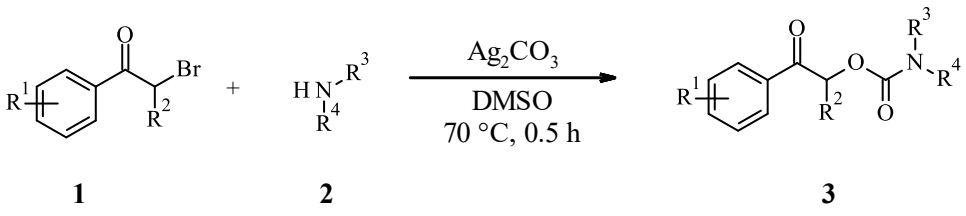
Figure 1: Carbamate-containing molecules in agrochemistry

1.2 A brief literature review on the chemistry of O-*β*-alkyl carbamates

In this section of the chapter, a concise summary of the synthesis, reactions, applications, and biological activities of carbamates was discussed, drawing from publications. These carbamate groups serve various purposes, such as acting as protecting groups, toxophores in biologically active compounds, or prodrugs designed to enhance biochemical properties.[8,9]

1.3 Our methodology for the synthesis of O-*β*-alkyl carbamate

This section of the chapter describes the results and discussion of a novel methodology for the synthesis of carbamate **3** from *α*-halopropiophenones **1** and secondary amines **2** using silver carbonate as a carbonate source under mild conditions (**Scheme 1**).

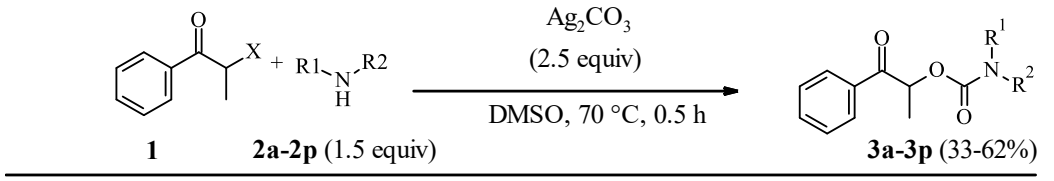


Scheme 1: O-*β*-alkyl carbamate synthesis from *α*-halopropiophenone derivatives

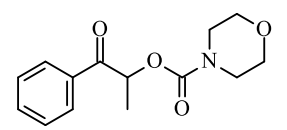
1.3.1 Substrate scope of O-*β*-alkyl carbamates with various secondary amines

In this section, the carbamate formation with a wide range of sixteen amines **2a–2p**, including symmetric and unsymmetric secondary amines, and cyclic and alicyclic secondary amines were explained. The secondary amines **2a–2o** were successfully converted into the corresponding carbamates, whereas *N*-methyl aniline **2p** under the optimized condition did not provide the desired carbamate (**Table 1,** examples **3a–3p**).

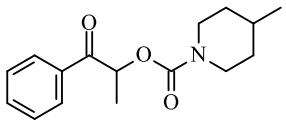
Table 1: Synthesis of carbamate with various secondary amines



1 **2a-2p** (1.5 equiv) **3a-3p** (33-62%)



3a



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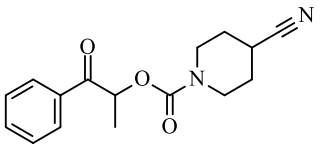

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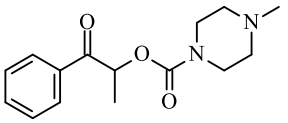

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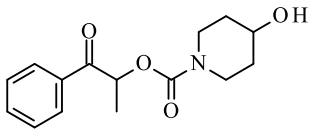

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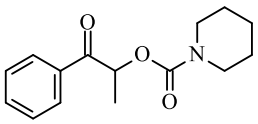

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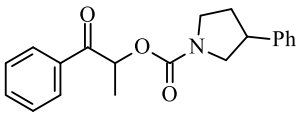

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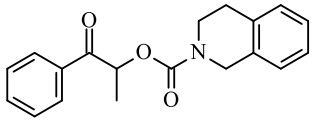

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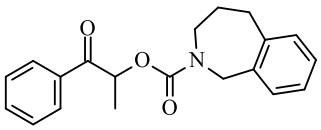

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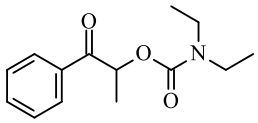

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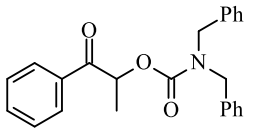

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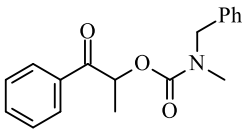

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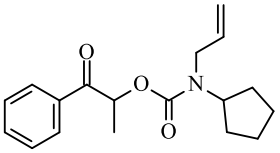

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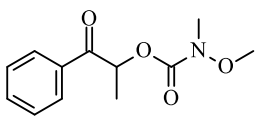

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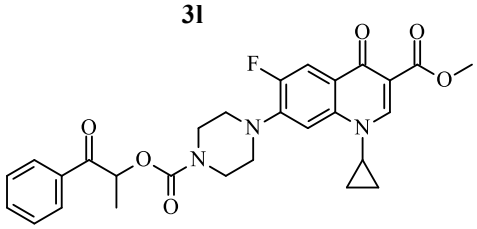

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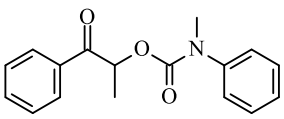
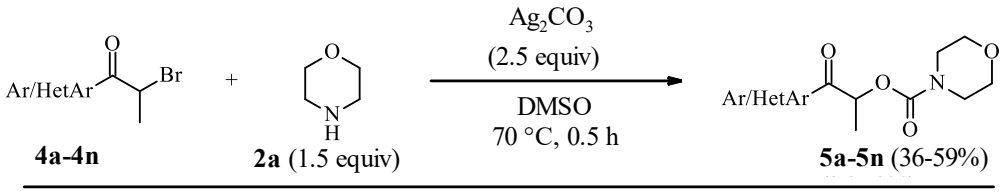


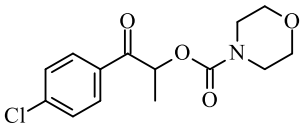
3p

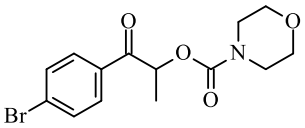
1.3.2 Synthesis of O-*β*-alkyl carbamates with various aryl/heteroaryls

In this section, a variety of *α*-bromoketones **4a–4n**, derived from aryl and heteroaryl substrates were examined (**Table 2,** examples **5a–5n**). To our delight, various propiophenone derivatives bearing electron-donating groups or electron-withdrawing groups such as methoxy, trifluoromethyl, methyl ester, nitro, halides (Cl, Br, I) at the ortho, meta, and para-positions of the benzene ring afforded the desired products in moderate to good yields. Notably, the heteroaryl *α*-bromo heteroaryl ketones containing quinoline **4l**, furan **4m**, and thiophene **4n** delivered the desired product.

Table 2: Synthesized carbamates with various aryl/heteroaryls




5a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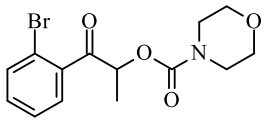
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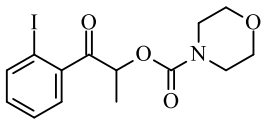
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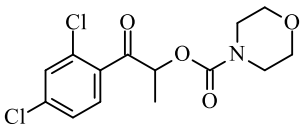
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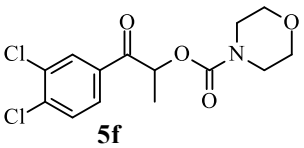
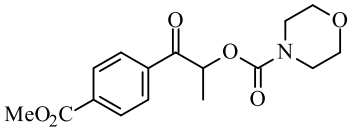

5f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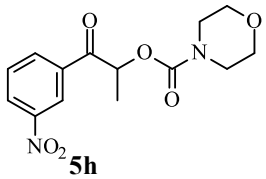
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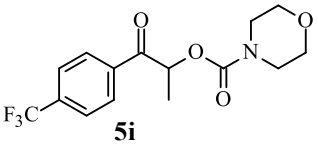
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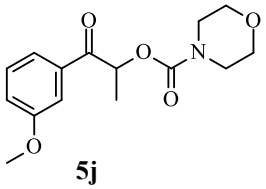
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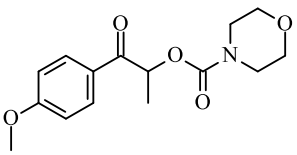
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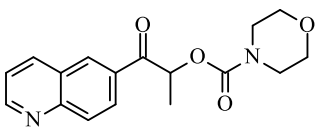
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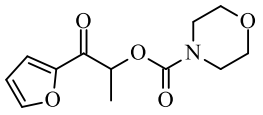
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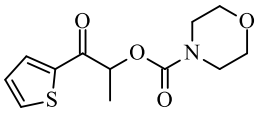
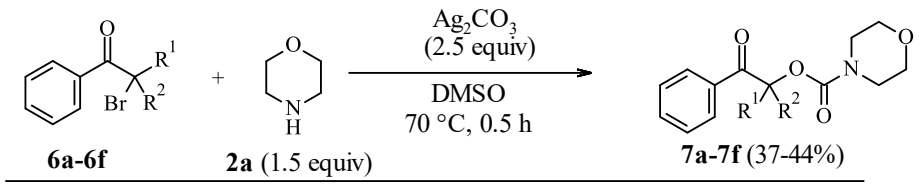
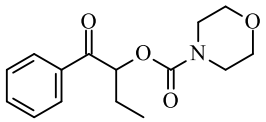

5n

1.3.3 Synthesis of O-*β*-alkyl carbamates with side chain variation

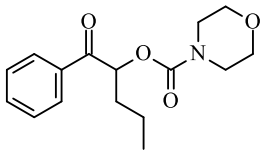
In this section, different *α*-bromoalkylphenones **6a–6f** were subjected to optimized reaction conditions. The effect of alkyl groups like methyl, ethyl, *n*-propyl, dimethyl, phenyl, and cyclic compound like tetralone was described in this section (**Table 3**; examples **7a–7f**). It was observed that mono alkylated *α*-bromoalkylphenones **6a–6b** resulted in the corresponding carbamate formation, whereas with no alkyl groups, with di alkyl and phenyl substituted *α*-bromoalkylphenones **6c–6f** resulted in no desired product formation.

Table 3: Synthesized carbamates with side chain variation





7a



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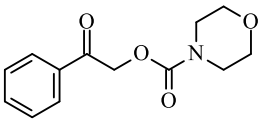

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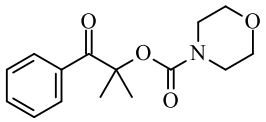

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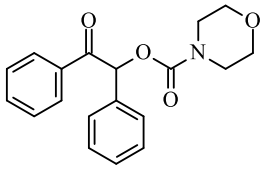

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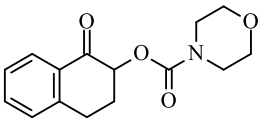
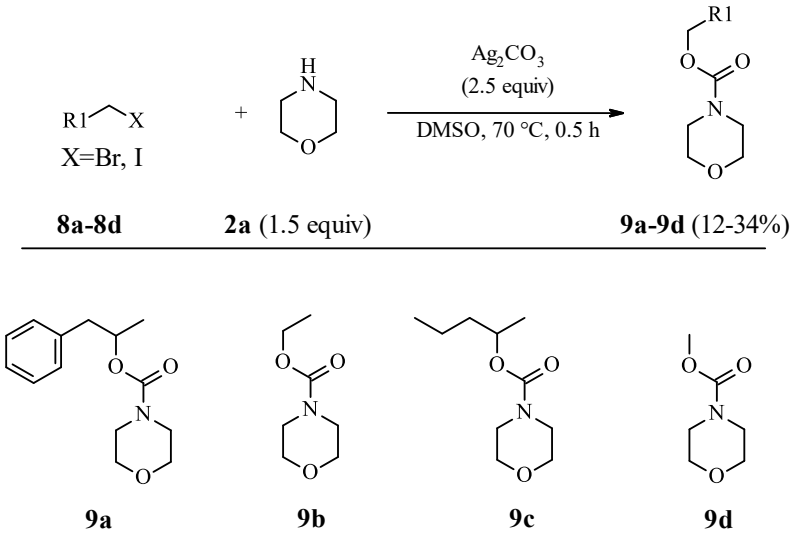


7f

1.3.4 Synthesis of carbamates with alkyl halide variation.

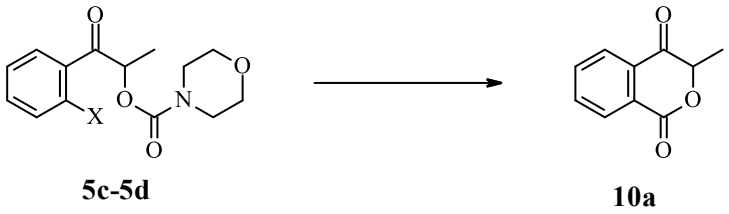
In this section, the importance of keto groups was explored. Halo substituted compounds like 2-bromopropylbenzene (**8a**), ethyl bromide (**8b**), methyl iodide (**8c**), and 2-bromopentane (**8d**) were explored for the carbamate formation. Among these compounds, only 2-bromopropylbenzene (**8a**) failed to produce the corresponding carbamate. On the other hand, compounds **8b**–**8d** successfully yielded the respective carbamates **9b**–**9d**. The results presented in this section conclusively demonstrate that the presence of a keto group is not essential for carbamate synthesis when employing optimized reaction conditions (**Table 4**).

Table 4: Synthesized carbamates with variation in α-haloalkanes



1.4 Application of carbamates towards the synthesis of isochromanones

In this section of the chapter, two of the synthesized carbamates **5c** and **5d** were used for the synthesis of isochromanone **10a** by anion generation, followed by cyclization. A few conditions were attempted but they were unsuccessful in achieving the synthesis of isochromanone.



Scheme 2 Synthesis of isochromanone from carbamate

1.5 Summary and conclusion

The major findings of this chapter are as follows:

1. The chapter presents an innovative approach for synthesizing O-β-alkyl carbamates utilizing silver carbonate as a carbonate source, employing mild reaction conditions.
2. A diverse range of α-halopropiophenones, encompassing both electron-donating and electron-withdrawing groups, were reacted with various secondary amines, yielding the corresponding O-β-alkyl carbamate derivatives in moderate to good yields.

3. Notably, the optimized reaction conditions exhibited excellent tolerance towards a variety of functional groups, including hydroxyl, methoxy, halides, nitrile, nitro, *N*-allyl, and ester groups.
4. This demonstrated the extensive substrate scope of various α-halopropiophenones when silver carbonate is employed as the carbonate source.
5. The application of these carbamates towards the synthesis of isochromanone was unsuccessful.

Chapter 2: Introduction to nitrogen-containing spiro heterocycles

This is an introductory chapter to chapter three, that provides a brief overview of the synthesis, applications, and biological activities of nitrogen-containing spirocyclic derivatives based on publications in chemical literature up to 2021. The various methods for synthesizing spirocyclic heterocycles, as well as their biological activities, have been discussed.

The spiroindolenine motif is found in many indole alkaloids which have a variety of biological activities such as antimalarial,[10] antimitotic, anticancer,[11] and insecticidal activity.[12] They are also useful as building blocks in the synthesis of veterinary products, dyes,[13] fine chemicals,[14] and a variety of other materials used in everyday life.[15] Few of the spiroindolines containing compounds are listed in **Figure 2**.

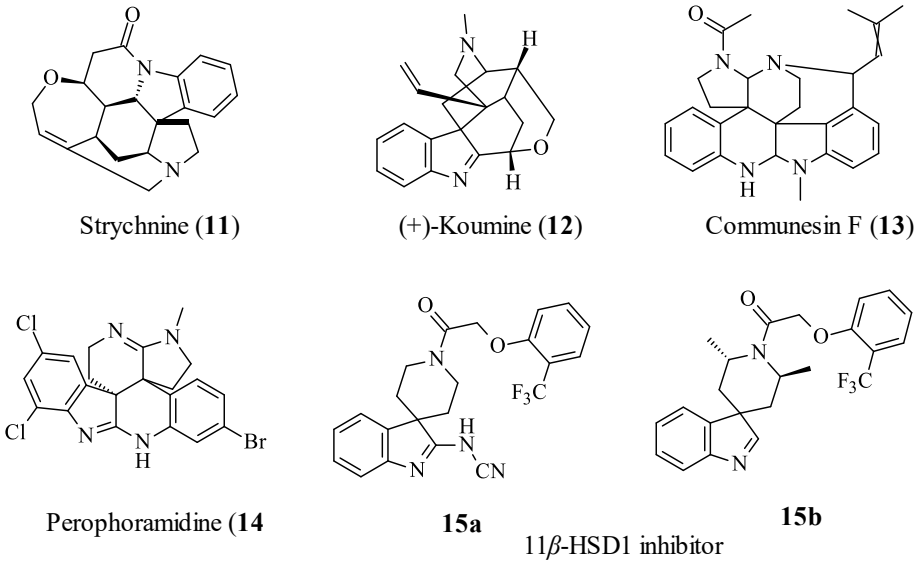


Figure 2: Spiroindole containing bioactive compounds

In this context, the current research work explored suitable methods to synthesize spiroindoline-containing fused heterocycles such as spiro[1,2,4]oxadiazoloindoles **17**, spiro[1,2,5]oxadiazinoindole **18** and spiro[1,2,4]triazinoindole **19** derivatives (**Figure 3**) and the characterized the newly synthesized compounds by ^{1}H NMR, ^{13}C NMR, FTIR, and HRMS analyses. Finally, the biological activity of these molecules in the field of crop protection was investigated. The design aspects and synthesis were explained in chapter three.

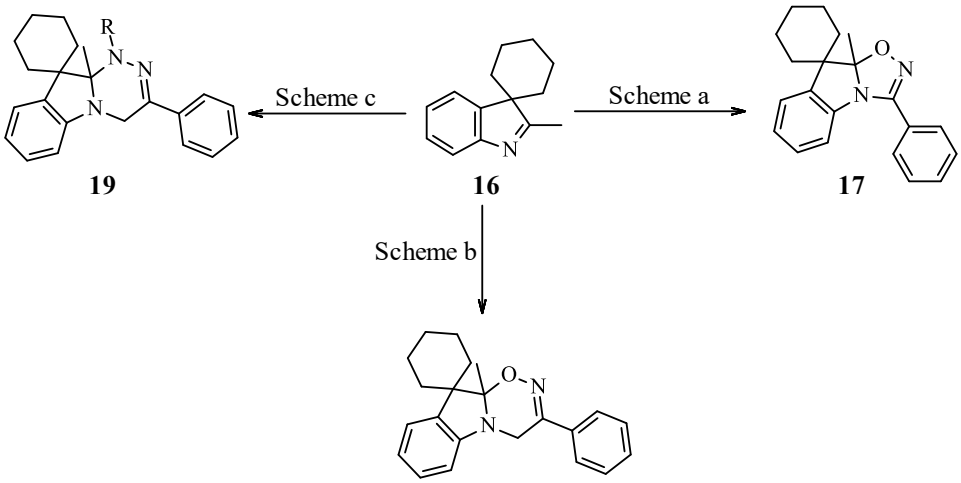


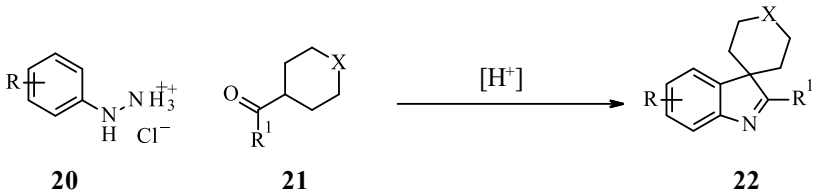
Figure 3: Spiroindoline containing fused heterocycles

Chapter 3: Design and synthesis of fused spiroindoline derivatives

This chapter explored the synthesis of spiroindolenines and their derivatization into fused spiroindole heterocycles. This chapter was further divided into four sections.

3.1 Synthesis of spiroindolenine derivatives

The first section of the chapter was about the synthesis of spiroindolenines from the phenyl hydrazines and ketone derivatives (**Scheme 3**) and the application of these spiroindolenines for the synthesis of other fused spiroindolines, which are explained in the later part of this chapter.

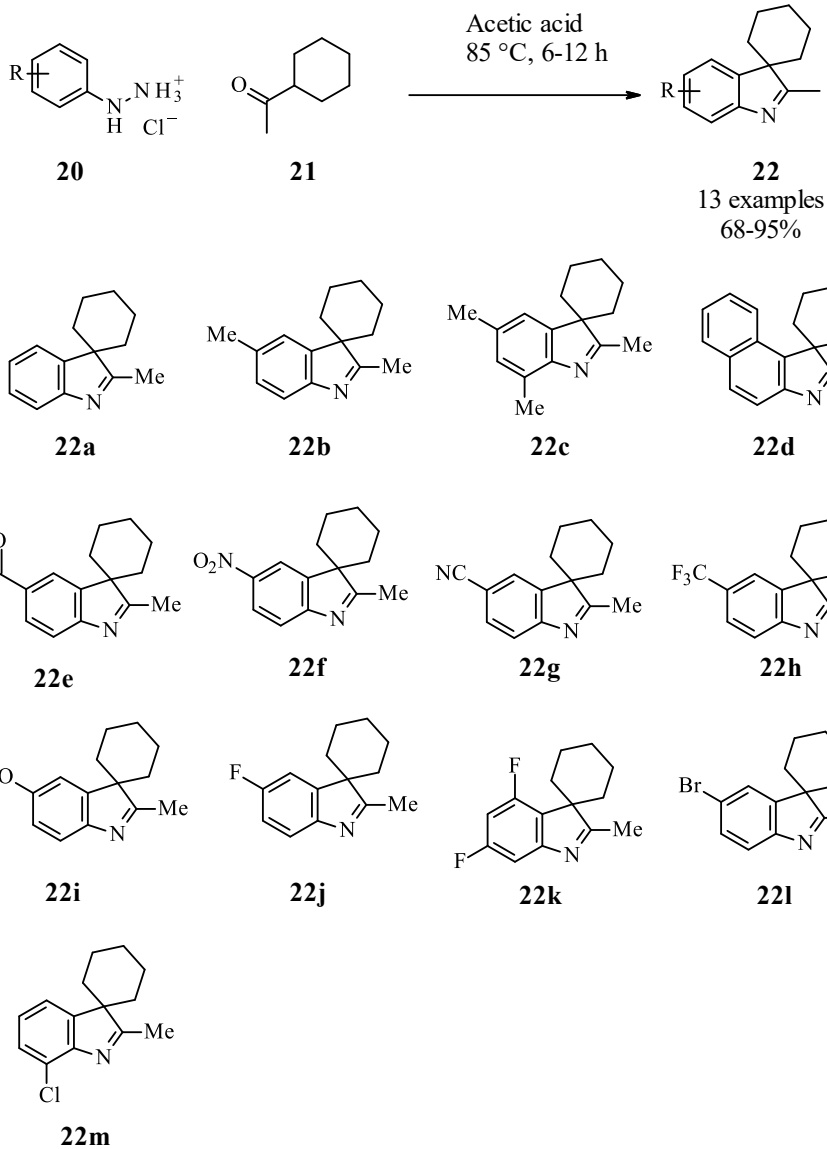


20 **21** **22**

Scheme 3: Synthesis of spiroindolenines from the phenyl hydrazines and ketone derivatives

In this study, thirteen spiroindolenines were synthesized by varying substitutions in the phenyl hydrazines (**Table 5**; examples **22a–22m**). The alkyl-substituted and benzo fused spiroindolenines were synthesized in good yield. The electron–withdrawing as well as electron–donating groups and halogen substituted spiroindolenines were synthesized in good yield.

Table 5: Synthesized spiroindolenine derivatives



20 **21** **22**
13 examples
68-95%

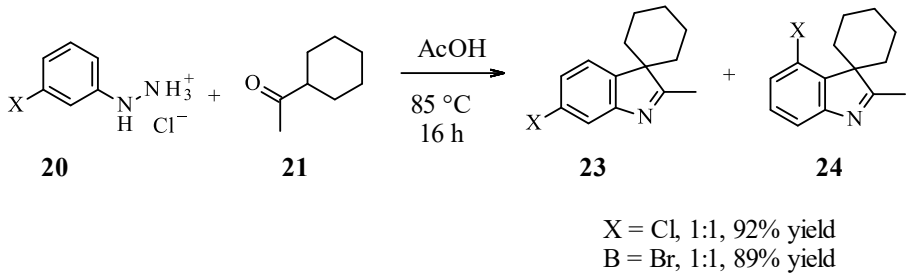
22a **22b** **22c** **22d**

22e **22f** **22g** **22h**

22i **22j** **22k** **22l**

22m

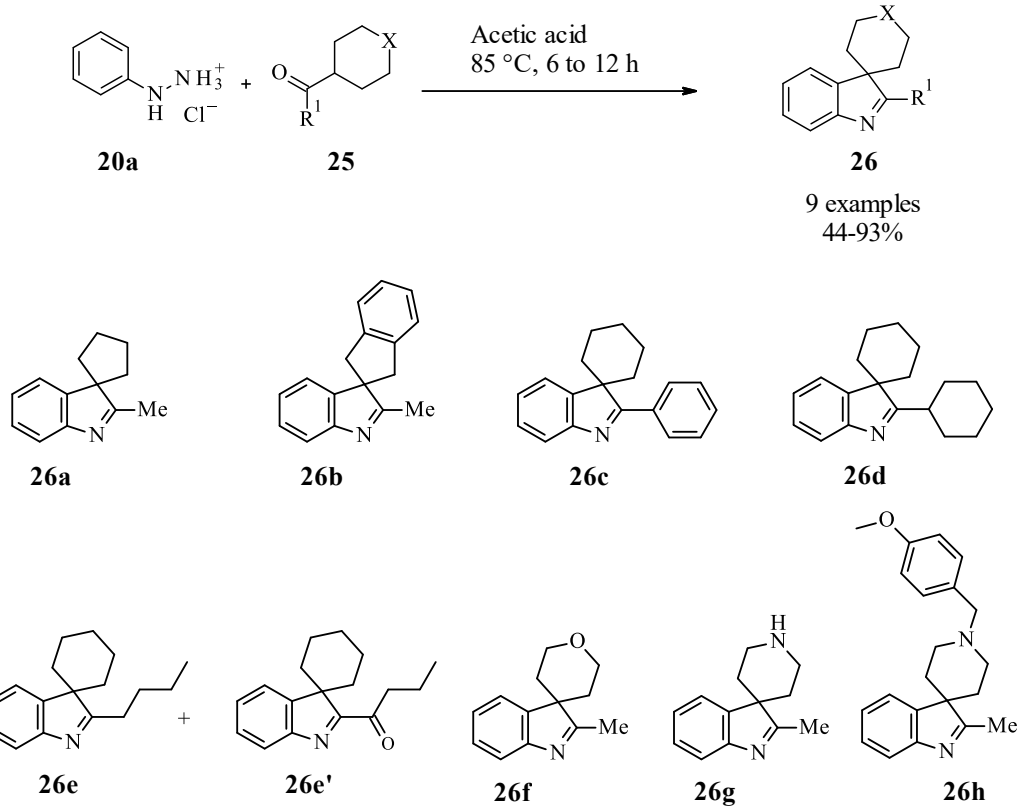
Regarding meta-substituted phenyl hydrazines, formation of two spiroindolenine products **23** and **24** were observed. Here 3-chlorophenylhydrazine hydrochloride **20n** and 3-bromophenylhydrazine hydrochloride **20o** were subjected to spiroindolization with methyl cyclohexyl ketone **21**. Both the hydrazines resulted in 1:1 ratio of spiroindolenines **23** and **24**, with yield 92% and 89% respectively (**Scheme 4**). This suggested that this method is not suitable for mono meta-substituted phenylhydrazines.



Scheme 4: General scheme for the spiroindolization of the meta-substituted phenylhydrazine

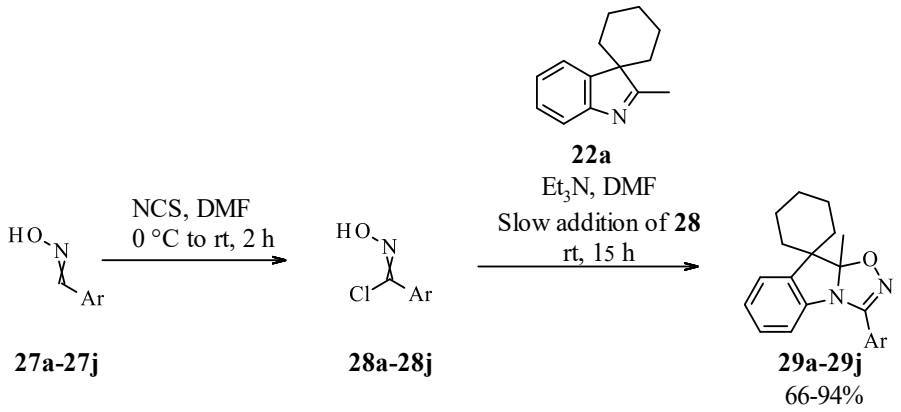
In this part of the chapter, various alkyl ketones **25** were reacted with phenyl hydrazine hydrochloride to get spiroindolenine with variation at the 2-position and different spiro-substituted indoles with 44–93% yield (**Table 6**).

Table 6: Synthesized spiroindolenine derivatives with various ketones



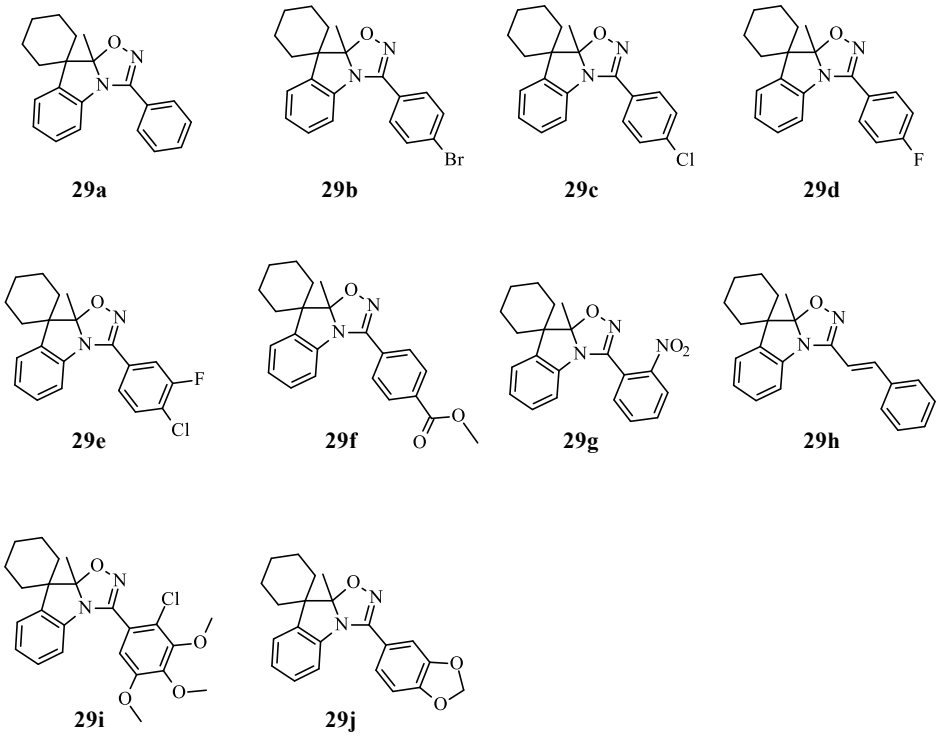
3.2 Design and synthesis of spiro[1,2,4]oxadiazoloindole derivatives

This section of the chapter explored the synthesis of spiro[1,2,4]oxadiazoloindoles **29** from spiroindolenine **22a** *via* [3+2] cycloaddition reaction. Here, 10 different oximes **27a**–**27j** were prepared, which are made to react with spiroindolenine *via* the formation of nitrile oxide. The nitrile oxides were prepared from their corresponding chloroaldoxime **28a**–**28j** and treated with spiroindolenines **22a** at room temperature to obtain the spiro[1,2,4]oxadiazoloindoles **29a**–**29j** in good to excellent yields (**Scheme 5)**. Aldoximes **27a**–**27j** with electron-donating and electron-withdrawing groups on the aryl ring successfully transformed into spiro[1,2,4]oxadiazoloindoles **29a–29j** with moderate to good yields under these optimized reaction conditions (**Table 6**; examples **29a–29j**).



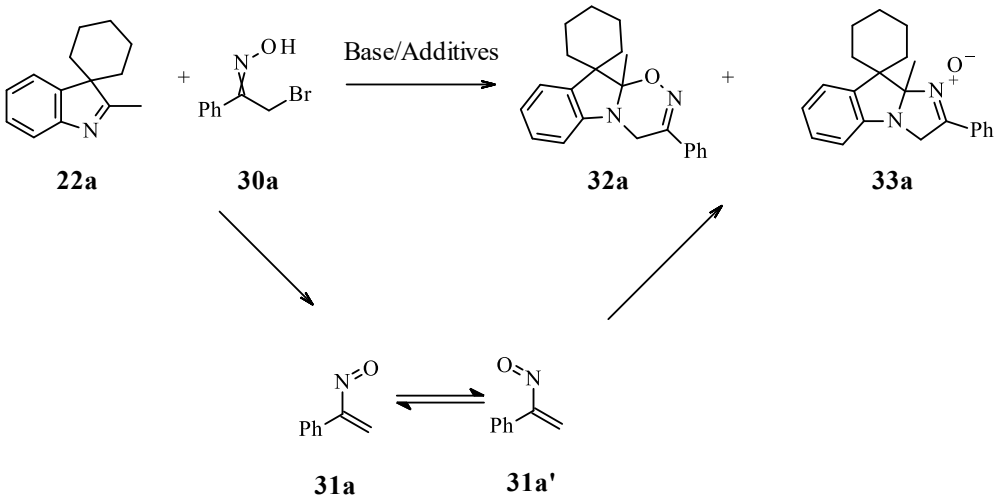
Scheme 5: Synthesis of spiro[1,2,4]oxadiazoloindole

Table 7: Synthesized spiro[1,2,4]oxadiazoloindole derivatives



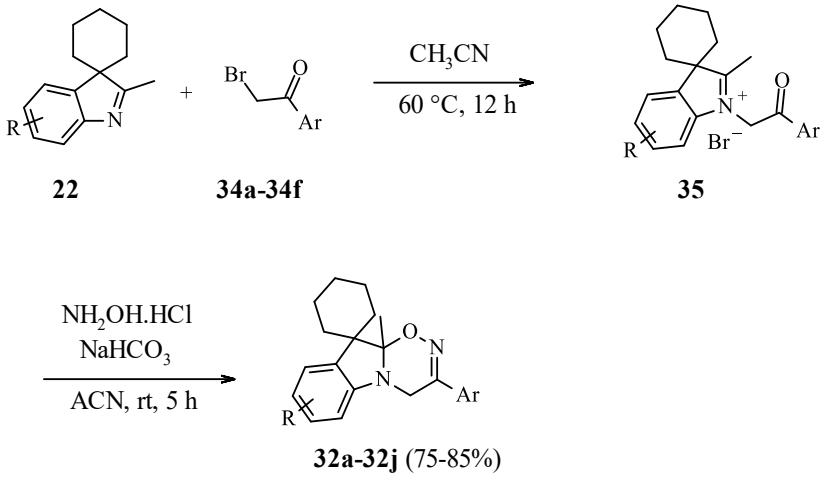
3.3 Design and synthesis of spiro[1,2,5]oxadiazinoindole derivatives

In this section, investigation of the cycloaddition reaction of *α*-halo ketoxime with spiroindolenine **29a–29j** to synthesize the spiro[1,2,5]oxadiazinoindole derivative **32a** was studied. First, *α*-bromo acetophenone oxime **30a** was made to react with spiroindolenine **22a**. During the reaction, intermediate nitroso styrene **31a** and **31a'** was formed *in situ*, which is expected to exist in both *cis* and *trans* forms. The [4+2] cycloaddition reaction resulted in the desired oxadiazine derivative **32a** *via* the *trans* form, whereas the [3+2] cycloaddition reaction led to the by-product imidazoline *N*-oxide **33a** *via* the *cis* form (**Scheme 6**). The use of additives like copper triflate in the [4+2] cycloaddition resulted in better conversion of **32a** with moderate yield. This study resulted in the formation of spiro[1,2,5]oxadiazinoindole derivative **32a** as a solo product in moderate yield in the presence of copper triflate *via* [4+2] cycloaddition.



Scheme 6: Reaction of *α*-bromo acetophenone oxime and spiroindolenine.

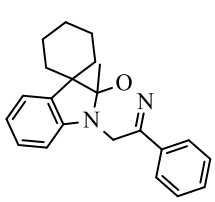
Also explored an alternate route for the synthesis of spiro[1,2,5]oxadiazinoindoles **32a** in good yield by replacing *α*-bromo ketoxime **30a** with *α*-bromo acetophenone **34a** *via* a two-step process **(Scheme 7**).



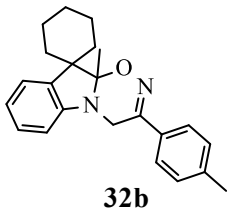
Scheme 7: Synthesis of spiro[1,2,5]oxadiazinoindoles from spiroindolenine and *α*-bromo acetophenone *via* two steps

The spiroindolenine **22a** was heated in acetonitrile along with *α*-bromo acetophenone **34a**.resulted in the formation of intermediate **35a,** was then treated with hydroxylamine sulfate at room temperature. Herein, 10 examples were prepared by varying both spiroindolenines and *α*-bromo acetophenones (**Table 8**; examples **32a–32j**).

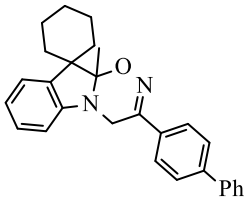
Table 8: Synthesized spiro[1,2,5]oxadiazinoindole derivatives



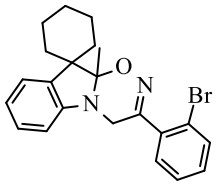
32a



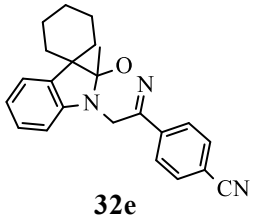
32b



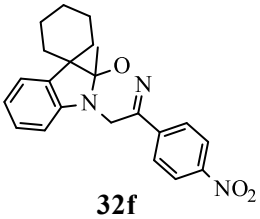
32c



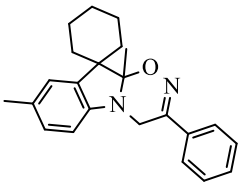
32d



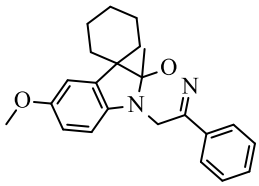
32e



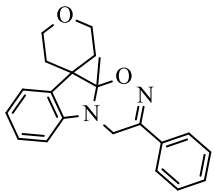
32f



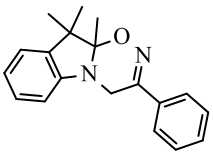
32g



32h



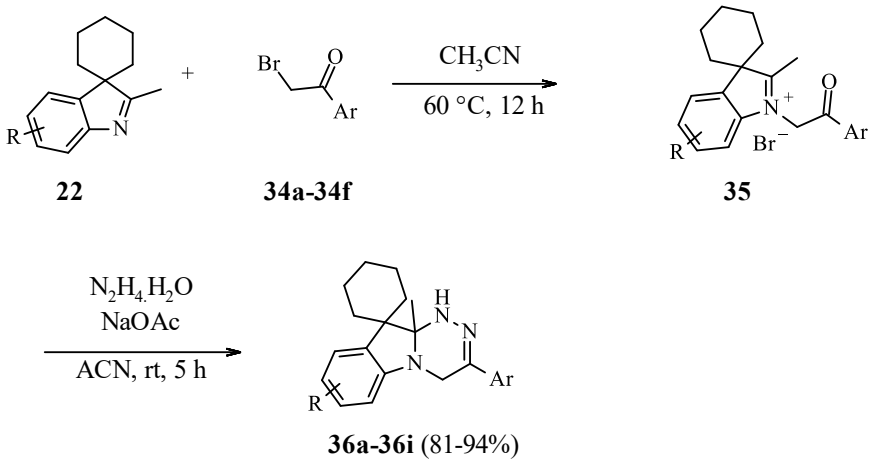
32i



32j

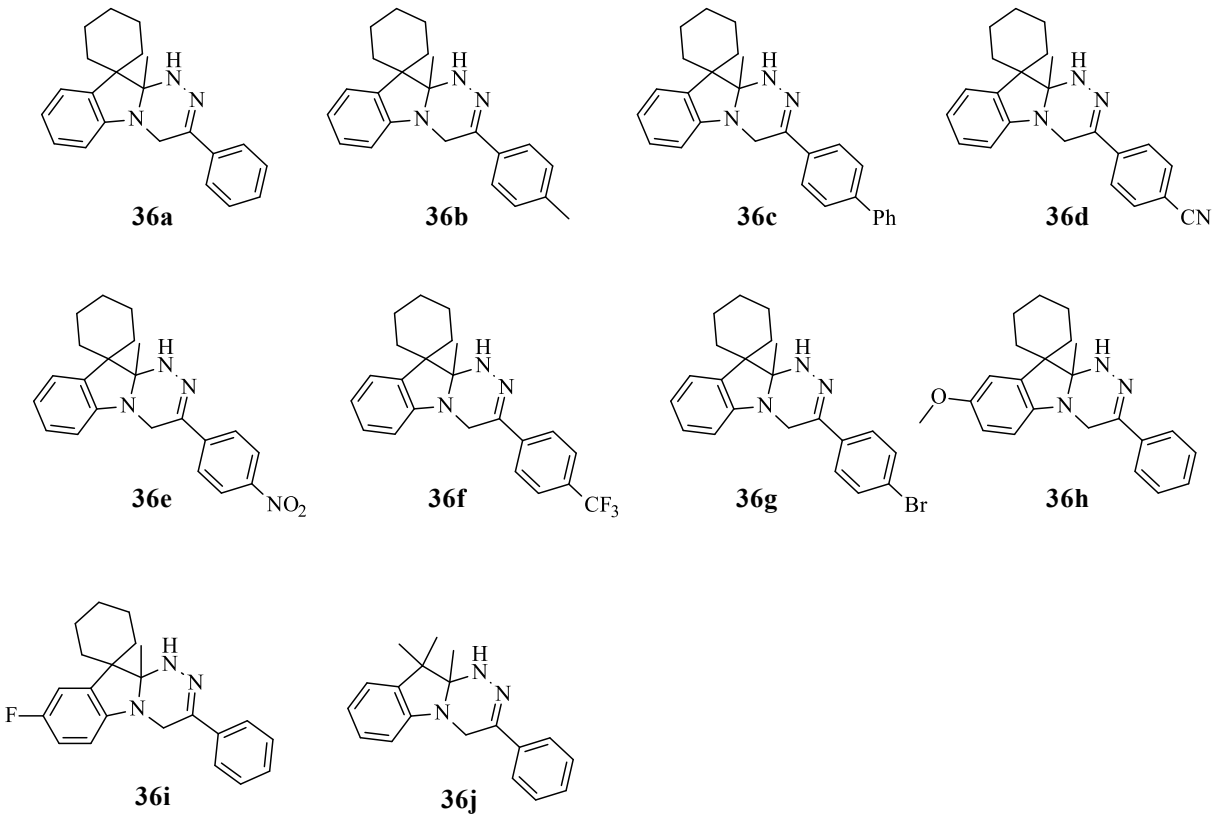
3.4 Design and synthesis of spiro[1,2,4]triazinoindole derivatives

In this section of the chapter, synthesis of spiro[1,2,4]triazinoindole derivatives was explored (**Scheme 7**). The synthesis of spiro[1,2,4]triazinoindole derivatives **36a–36i** was achieved in good yield from spiroindolenines **22** and *α*-bromoacetophenone **34a** *via* the salt **35** formation, followed by treatment with hydrazine hydrate at room temperature (**Table 8**; examples **36a–36j**).



Scheme 8: Synthesis of spiro[1,2,4]triazinoindole from spiroindolenine and α-bromo acetophenone

Table 9: Synthesized spiro[1,2,4]triazoloindoles derivatives



3.5 Summary & Conclusion

A summary of the whole study is made, and conclusions are drawn based on the study.

1. This is the first report on the synthesis of novel spirofused heterocycles like spiro[1,2,4]oxadiazole, spiro[1,2,5]oxadiazinoindole and spiro[1,2,4]triazinoindole formation using a two-step process in good yield.
2. The structures of all the new compounds were established based on ^{1}H and ^{13}C NMR, FTIR, and mass spectrometry data. The structures of the novel compounds were confirmed by 2D NMR analysis and single X-ray crystallography.
3. A plausible mechanism for cycloaddition for the synthesis of spiro[1,2,5]oxadiazine from spiroindolenine and α-bromoacetophenone was proposed.
4. Various substituted α-bromo acetophenones and spiroindolenines were subjected to these reaction conditions.
5. 10 Examples each were made in spiro[1,2,4]oxadiazoloindole, spiro[1,2,5]oxadiazinoindole and spiro[1,2,4]triazinoindole were made with moderate to good yield.
6. All the synthesized compounds were analyzed in the crop protection field for fungicidal, insecticidal, and herbicidal activity.

Chapter 4: Biological evaluation of carbamates and spiroindoline derivatives in the field of crop protection

This chapter describes the biological assay of the synthesised novel fused spiroindoline derivatives and carbamate derivatives in the crop protection field for fungicidal, insecticidal, and herbicidal activities.

Table 10: Discovery of early screening results of carbamate derivatives

	Fungicide Assays							Herbicide Assays		Insecticide Assays		
Compound Number	***Uromyces viciae-fabae*** *(bean - preventative)*	***Botryotinia fuckeliana***	***Gibberella zeae***	***Phytophthora capsici***	***Zymoseptoria tritici*** *(minimal media)*	***Zymoseptoria tritici*** *(rich media)*	***Pythium ultimum***	***Arabidopsis thaliana***	***Digitaria sanguinalis***	***Plutella xylostella*** *(Larval mortality)*	***Myzus persicae*** *(Mixed population mortality)*	***Tetranychus urticae*** *(Mixed population mortality)*
3a	0	0	0	0	0	0	0	0	25	0	0	0
3d	0	100	100	0	0	0	0	0	0	0	0	0
3n	0	95	62	0	0	0	0	0	0	0	0	0
3o	0	80	0	0	0	0	0	0	10	0	0	0
5d	0	0	0	0	0	0	50	0	0	0	0	0
5g	0	0	0	0	0	0	0	0	0	0	0	67
5j	27	50	0	0	0	0	0	0	0	0	0	0
7a	27	28	0	0	0	0	0	0	0	0	0	0

Table 11: Discovery of early screening results of spiroindolenine derivatives

	Fungicide Assays							Herbicide Assays		Insecticide Assays		
Compound Number	***Uromyces viciae-fabae*** *(bean - preventative)*	***Botryotinia fuckeliana***	***Gibberella zeae***	***Phytophthora capsici***	***Zymoseptoria tritici*** *(minimal media)*	***Zymoseptoria tritici*** *(rich media)*	***Pythium ultimum***	***Arabidopsis thaliana***	***Digitaria sanguinalis***	***Plutella xylostella*** *Larval mortality)*	***Myzus persicae*** *(Mixed population mortality)*	***Tetranychus urticae*** *(Mixed population mortality)*
22a	0	0	0	35	0	0	90	0	0	0	0	0
22b	0	70	0	70	28	0	0	10	10	0	0	0
22c	0	0	0	70	0	28	27	0	10	0	0	33
22d	0	0	0	0	0	100	0	50	50	17	0	0
22f	0	90	35	0	0	0	0	0	0	0	0	0
22i	0	35	0	28	0	0	0	35	10	0	40	0
22j	0	0	0	55	0	0	90	0	20	0	0	0

22l	0	0	0	0	0	0	0	0	0	0	40	0
22m	0	0	0	2	0	0	55	20	0	0	0	0
26a	0	0	0	70	0	0	80	0	0	0	0	0
26g	0	90	0	0	28	62	0	10	25	33	0	0

Table 12: Discovery of early screening results of spiro fused indole derivatives

Compound Number	Fungicide Assays							Herbicide Assays		Insecticide Assays		
	Uromyces viciae-fabae *(bean - preventative)*	***Botryotinia fuckeliana***	***Gibberella zeae***	***Phytophthora capsici***	***Zymoseptoria tritici*** *(minimal media)*	***Zymoseptoria tritici*** *(rich media)*	***Pythium ultimum***	***Arabidopsis thaliana***	***Digitaria sanguinalis***	***Plutella xylostella*** *(Larval mortality)*	***Myzus persicae*** *(Mixed population mortality)*	***Tetranychus urticae*** *(Mixed population mortality)*
29a	0	0	0	0	0	0	0	0	0	0	0	0
29b	0	0	0	0	0	0	28	10	0	0	0	0
29e	0	0	0	0	0	0	0	0	0	33	0	0
29h	0	0	0	0	0	0	0	0	0	33	0	0
32a	0	0	0	0	0	0	0	0	0	0	0	67
32b	0	0	0	28	0	0	100	10	0	53	0	33
32d	0	0	0	0	0	0	0	0	0	0	0	33
32e	0	0	0	63	0	0	0	25	0	0	0	66
32f	0	0	0	63	0	0	0	0	0	17	0	0
32h	0	0	0	0	0	0	0	10	0	0	0	33
36a	0	0	0	80	0	0	0	0	0	0	0	0
36b	0	0	0	90	0	0	0	0	0	100	0	0
36e	0	0	0	0	0	0	0	0	0	40	0	0
36g	0	0	0	0	0	0	0	0	0	80	0	0
36h	0	0	0	0	0	0	0	25	25	33	0	0
36j	0	0	0	0	0	0	70	0	90	0	0	0

Summary

A summary of the whole study is made, and conclusions are drawn based on the study.

The major finding of this chapter is as follows:

(i) Three carbamate compounds (**3d**, **3n** and **3o**) showed fungicidal activity against *Botryotinia fuckeliana* species and one carbamate **3d** showed fungicidal activity against *Gibberella zeae* (**Table 10**).

(ii) Three spiroindolenines compounds (**22b**, **22f** and **26g**) showed moderate fungicidal activity with 70-90% against *Botryotinia fuckeliana*. The spiroindolenines **22b**, **22c**, **26a** showed fungicidal activity with 70% control against *Phytophthora capsici*. Spiroindolenine 100d showed complete control against *Zymoseptoria tritici (rich media).* Three spiroindolenines **22a**, **22j** and **26a** showed 80-90% control against *Pythium ultimum* (**Table 11**).

(iii) The synthesized spiro[1,2,4]oxadiazoloindoles were inactive in all three indications (**Table 12**; entries 1–4)

(iv) The spiro[1,2,5]oxadiazinoindoles **32e** and **32f** showed 63% control against *Phytophthora capsica*. Whereas the compound **32b** showed complete control against *Pythium ultimum*. The compounds **32a** and **32e** showed 66-67% mortality against *Tetranychus urticae* species. Only compound **32b** showed 53% mortality against *Plutella xylostella* (**Table 12**; entries 5-10).

(v) The spiro[1,2,4]triazinoindoles **36a** and **36b** showed 80-90% control against *Phytophthora capsica*. Compound **36j** showed 70% control against *Pythium ultimum* and it also showed 90% herbicidal activity against *Digitaria sanguinalis*. In the case of the insecticidal assay, compound **36b** showed 100% mortality against *Plutella xylostella* whereas compound **36g** showed 80% mortality against *Plutella xylostella* (**Table 12**; entries 11-16).

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List of Publications:

A] In National/International Journals

1. Synthesis of carbamate from alkyl bromides and secondary amines using silver carbonate. **Vanitha Acharya**, Sanjib Mal, Jagadeesh P. Kilaru, Mark G. Montgomery, Sudhindra H. Deshpande, Ravindra P. Sonawane, Bhanu N. Manjunath, and Sitaram Pal. *Eur. J. Org. Chem.* **2020**, 378–387.

B] In National/International Conference Proceedings

1. CO_2 free Synthesis of Carbamates from Alkyl Bromides and Secondary Amines using Silver Carbonate. **Vanitha Acharya**, Sanjib Mal, Jagadeesh P. Kilaru, Mark G. Montgomery, Sudhindra H. Deshpande, Ravindra P. Sonawane, Bhanu N. Manjunath, Sitaram Pal. Presented in the XV J-NOST 2019 Conference held at Department of Chemistry, University of Delhi, Delhi-during 18th to 21st October 2019. **Abstr. No: PP -83**.
2. Synthesis and Biological Activity of Spiroindolenines and Spiro[1,2,4] Oxadiazoloindoles. **Vanitha Acharya**, Jagadeesh P Kilaru, Venunath Hapse, Manish Parab, Sujit Ghorai and Sitaram Pal. Presented at 29th CRSI-National Symposium in Chemistry and CRSI-ACS Symposium Series in Chemistry held at Indian Institute of Science Education and Research (IISER) Mohali, during July 07-09, 2022. **Abstr. No: P-311.**
3. Silver carbonate mediated synthesis of carbamate from alkyl bromides and secondary amines. **Vanitha Acharya**, Bhanu N. Manjunath, Sitaram Pal. **Oral Presentation**, presented in the International Conference on Aggregation-Induced Emission from Fundamental to Applications 2022, held at Department of Chemistry, BITS Pilani, KK Birla Goa Campus, Goa during 16th to 18th December 2022. **Abstr. No: SL 7.**

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